REMARKS

Reconsideration and allowance are requested.

Claims 22, 25-36 and 40-43 are pending. Claims 23-24 and 37-39 are canceled without prejudice or disclaimer because their limitations are redundant in view of the amendment of independent claims 22 and 27, respectively.

Claims 25 and 40 were withdrawn from consideration by the Examiner; their rejoinder is requested.

Here, cancer cells are limited to "human" cancer cells (see paragraph [0014] of the specification) and the non-human animal is limited to a "nude mouse" or "nude rat" (see paragraph [0024] of the specification). Moreover, the polymer is limited to "a homo- and/or co-polymer of N-isopropylacrylamide") (see paragraphs [0016] and [0021] of the specification). New claims 42-43 are supported by original claim 4.

Claim Objection

Claim 27 was objected to by the Examiner. Adoption of his suggestions to amend the claim moots this objection. Therefore, withdrawal of the objection is requested.

35 U.S.C. 112 – Written Description

Claims 22-24, 26-39 and 41 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Although they disagree with the Examiner's allegations, Applicants moot portions of this rejection by deletion of challenged limitations in claims 22 and 27 solely to advance prosecution in this application.

Here, the polymer is "a homo- and/or co-polymer of N-isopropylacrylamide") (see paragraphs [0016] and [0021] of the specification). Hydration forces that are "weak" or "strong" are described in paragraphs [0007] and [0008] of the specification, which also describe that temperature changes the polymer's hydration force. Finally, transplantation of the cultivated and detached cells to "a specified site of an animal on which transplantation is to be performed" is described in the Abstract.

Support for claims 28-39 and 41 is found in original claims 2-3, 5-10 and 16 as well as paragraph [0014] of the specification.

Withdrawal of the new matter rejection made under Section 112, first paragraph, is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 22-24, 26-39 and 41 were rejected under Section 112, first paragraph, because allegedly the specification "does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed." Applicants traverse.

First, the polymer is limited to "a homo- and/or co-polymer of N-isopropylacrylamide" in claims 22 and 27 (cf. the bottom of page 7 of the Office Action). This amendment is made solely to advance prosecution in this application and is not an admission that the objection was proper.

Second, the claimed invention is limited to use of human cancer cells in a nude mouse or nude rat (cf. the middle of page 9 of the Office Action). This amendment too is made solely to advance prosecution in this application and is not an admission that the objection was proper.

Third, a test substance is administered then selected in accordance with claim 26 based on its ability to reduce the volume and/or weight of a tumor formed from the sheet of human cancer cells. Such administration and selection do not require undue experimentation for a skilled artisan to practice the claimed invention in accordance with paragraph [0026] of the specification as well as Example 3. It was alleged on pages 10-11 of the Office Action that "specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified" would require undue experimentation. But since Applicants submit that such techniques would be known to a skilled artisan, if this rejection is maintained, the Examiner is respectfully requested to

cite evidence or reasoning that the skilled artisan could not utilize conventional techniques to select anti-tumor agents in accordance with Applicants' invention.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

35 U.S.C. 112 – Definiteness

Claims 22-24, 26-39 and 41 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Although they disagree with the Examiner's allegations, Applicants moot portions of this rejection by deletion of challenged limitations in claims 22 and 27 solely to advance prosecution in this application.

Here, the hydration force is weak or strong depending on temperature (see paragraphs [0007] and [0008] of the specification). A change from weak hydration force to strong hydration force (they forces are "weak" or "strong" relative to each other) permit detaching the cultivated cancer cells in accordance with Applicants' invention. Similarly, a change in temperature can shift the cell culture support from hydrated to dehydrated. Their teachings in paragraph [0021] of the specification, along with Examples 1 and 2, provide sufficient guidance to the skilled artisan for the temperature-responsive properties of poly(N-isopropylacrylamide).

Antecedent basis in claim 29 is corrected. The phrase "a human cancer cell sheet to be transplanted is prepared in a specified shape of a specified size" means that the human cancer cell sheet is prepared in accordance with the site on the animal to which the human cancer cell sheet is transplanted. Thus, "the size and/or shape of cancer tissue in the nude mouse or nude rat is controlled" by preparation of the human cancer cell sheet.

For claims 31 and 33, the definitions of "transplantable" and "untransplantable" are clear from paragraph [0014] of the specification. If this rejection is maintained, the Examiner is respectfully requested to clarify what is meant by alleging "the metes and bounds of <u>when</u> a cancer cell is from an 'untransplantable' cell line" (emphasis added) as regards claim 33.

Claim 35 further limits the subject matter of the independent claim because the human cancer cells may not be collected from a living tissue (see "alternatively, they include, but are not limited to, cell lines" in paragraph [0014] of the specification).

Claim 41 clearly requires administering a test substance.

Withdrawal of this rejection made under Section 112, second paragraph, is requested because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 27-31, 33, 35 and 37-39 were rejected under Section 102(b) as allegedly anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994). Applicants traverse.

Koezuka describes a method for culturing human cancer cells by using a thermo-responsive polymer (PNIPAAm), as well as a substrate conjugated collagen and this polymer. The substrate described therein (i.e., a mixture of collagen and PNIPAAm) corresponds to the cell culture support of Applicants' invention but is not used in the manner required by their claims. In other words, Koezuka's substrate is a PNIPAAm-collagen substrate, which is different from the cell culture support used in Applicants' process. According to the cited document, the PNIPAAm-collagen substrate is changed from a solid phase to a liquid phase, and this change detaches the cultured cells for recovery. But Koezuka's cell culture support does not satisfy the requirement of Applicants' claims to change the polymer's hydration force from weak to strong by shifting the temperature of cultivation. Further, the cited document suggests that the human cancer cell lines are cultured in a gel. In contrast, Applicants' cell culture support as used in their claimed process never changes to a liquid phase. Therefore, Koezuka does not anticipate claims 27-31, 33, 35 and 37-39.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. At 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 22-24, 27-31, 33, 35 and 37-39 were rejected under Section 103(a) as allegedly unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai (JP 05/192138). Applicants traverse.

As discussed above, Koezuka discloses a mixture of PNIPAAm and collagen for use as a substrate (i.e., a PNIPAAm-collagen substrate) to cultivate human cancer cells. Although the PNIPAAm-collagen substrate corresponds to the cell culture support

of Applicants' invention, Koezuka's substrate is not used in the manner required by their claims. In other words, the substrate of the primary document is a PNIPAAm-collagen substrate, which is different from the cell culture support used in Applicants' process. According to the primary document, the PNIPAAm-collagen substrate is changed from a solid phase to a liquid phase by changing the temperature, and this change detaches the cultivated cells from the cell culture support. Koezuka's cell culture support does not satisfy Applicants' requirement for a temperature shift that changes the hydration force from weak to strong (see also "the polymer makes a sudden shift from a dehydrated to a hydrated state" in paragraph [0015] of the specification). Further, the primary document suggests that the human cancer cell lines are cultured in a gel. In contrast, Applicants' cell culture support as used in their claimed process never changes to a liquid phase. Thus, Koezuka's use of a PNIPAAm-collagen substrate is not analogous to use of a cell culture support according to claims 22-24, 27-31, 33, 35 and 37-39.

Sakai describes a method of cultivating skin cells comprising: preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached.

Sakai teaches, however, that this method is applied only to skin cells. It neither teaches nor makes obvious that the method can be applied to other normal types of cell or any kind of cancer cell. Moreover, Sakai does not make obvious that when detached cancer cells are in the form of a sheet, they are brought into contact with a carrier at the time the cultivation is completed and the cancer cells can then be detached intact from a cell culture support together with the carrier.

In view of the above, the cited documents teach away from Applicants' invention and show a lack of a reasonable expectation of success to make their claims. Thus, the claimed invention is patentabile over Koezuka in view of Sakai, which does not address the deficiencies of the primary document. As taught in paragraph [0004] of the specifica-

tion, transplanted cancer cells obtained by prior art techniques have poor take and the size and weight of the transplanted sheet of cancer cells varies so greatly from one animal to another that evaluation of various anti-cancer agents to reveal any significant differences in their efficacy is difficult.

The object of the present invention is to provide a new non-human animal model free from the problems of the prior art (see paragraph [0004] of the specification). The present invention is characterized in that cancer cells can be transplanted efficiently by using a sheet of cancer cells. Such efficient transplantation of cancer cells into a non-human animal could not been achieved using prior art techniques (see paragraph [0007] of the specification).

With regard to common general knowledge in the art as of March 4, 2004 (i.e., the filing date of the priority application) and whether there was a reasonable expectation of success, only the following cancer cell-transplanted animals were known (see paragraph [0003] of the specification):

1) knockout mice deprived of anti-oncogenes such as APC and p53, and

2) animals in which cancer has been developed by various methods such as the use of chemicals and other carcinogenic agents and direct transplantation of human cancer cells of interest.

But use of these animals raised the following problems (see paragraphs [0003] and [0004] of the specification). Among these animals, anti-oncogene knockout mice require fairly sophisticated (and expensive) genetic manipulation. Cancer development with carcinogenic agents requires a prolonged time to accomplish. Transplanting cancer cells has the advantage of giving experimental results in a short period of time. On the other hand, in the prior art, the transplanted cancer cells have poor take and the size and weight of the transplanted cancer tissue vary so greatly from one animal to another that evaluation of various anti-cancer agents involves difficulty in revealing any significant differences in their efficacy. Reasons for this defect include the poor take of the transplanted cancer cells and the leakage of the cancer cells suspension from the site of transplantation. Therefore, Applicants believed it was desirable to improve functions of the cells to be transplanted.

The present invention was made to solve the foregoing drawbacks. As taught in paragraph [0015] of the specification, Applicants' present invention is characterized by the following features.

If human cancer cells are cultivated on a cell culture support coated on a surface with a polymer (the hydration force of which changes in a temperature range of 0-80°C), the cultivated cells can be detached from the support without a proteolytic enzyme (e.g., trypsin) being used. Only a simple change in the cultivation temperature is required. As a result, the detached cell sheet is free from damage it would have received if treated with a proteolytic enzyme such as trypsin. Since detachment of the cultivated human cancer cells involves no enzyme treatment, the adherent protein remains intact and assures good take after transplantation. If the human cancer cells are in a sheet form, there is another advantage in that the leakage of a cell suspension from the site of transplantation is effectively suppressed to allow for efficient preparation of a human cancer cell-transplanted animal.

As illustrated in Examples 1 and 2 of Applicants' specification, their invention has made it possible to form cancer tissue in a cancer cell-transplanted animal in a manner superior to the prior art. None of the documents cited thus far taught or made obvious such an advantageous technique that efficiently produces a human cancer cell-transplanted animal by directing attention to the properties of the cells recovered without proteolytic enzyme treatment.

The present invention has made it possible to obtain a non-human animal model in which size and/or shape of cancer tissue in the animal can be controlled by preparing a sheet of the cancer cells in a specified size and/or shape. Therefore, Koezuka in view of Sakai would not have made the claimed process obvious with a reasonable expectation of success at the time Applicants' invention was made.

Claims 22-24, 27-31, 33, 35 and 37-39 were rejected under Section 103(a) as allegedly unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai (JP 05-192138) and Hirose et al. (Biomacromolecules 1:377-381, 2000). Applicants traverse.

The disclosures of Koezuka and Sakai were discussed above. This combination does not make obvious Applicants' invention because of the deficiencies that were also

previously discussed. Further, Hirose's disclosure is not sufficient to remedy such failure because it does not address of the obviousness of cultivating human cancer cells, their detachment, and subsequent transplantation in a non-human animal. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved. Therefore, Koezuka in view of Sakai and Hirose would also not have made the claimed process obvious with a reasonable expectation of success at the time Applicants' invention was made.

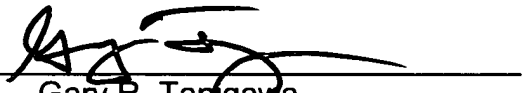
Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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